PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 20 April 2000 (20.04.00)	
International application No.: PCT/EP99/07634	Applicant's or agent's file reference: PCT1072-1996
International filing date: 12 October 1999 (12.10.99)	Priority date: 13 October 1998 (13.10.98)
Applicant: RANSBERGER, Karl et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

10 January 2000 (10.01.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

3

Applicant's or agent's file reference PCT107203196/sm	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/07634	International filing date (*day/month/year*) 12 October 1999 (12.10.99)	Priority date (*day/month/year*) 13 October 1998 (13.10.98)
International Patent Classification (IPC) or national classification and IPC A61K 38/48		
Applicant MUCOS PHARMA GMBH & CO.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10 January 2000 (10.01.00)	19 January 2001 (19.01.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP99/07634

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-18, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-8, filed with the letter of 02 October 2000 (02.10.2000),
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/6-6/6, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-7

because:

☒ the said international application, or the said claims Nos. 1-7 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See annex

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Claims 1 to 7 concern subject matter which, in the opinion of this Examining Authority, falls under PCT Rule 67.1(iv). Therefore no expert opinion concerning the industrial applicability of the subject matter of these claims will be prepared (PCT Article 34(4)(a)(i)).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	5, 6	YES
	Claims	1 - 4, 7, 8	NO
Inventive step (IS)	Claims		YES
	Claims	1 - 8	NO
Industrial applicability (IA)	Claims	See Box V, point 2	YES
	Claims		NO

2. Citations and explanations

1. For the following reasons, the subject matter of Claims 1 to 4, 7 and 8 is not considered novel within the meaning of PCT Article 33(1) and (2):

D2 (WO-A-96/00082) shows the ability of bromelain to act as a modulator for intracellular signal transmission, in particular for intracellular signal paths which are dependent on inositol phosphates, protein kinases and/or phosphatases. This includes, in particular, the blockading of signals which are necessary for the proliferation of T cells and the inhibiting of cytokine production by bromelain (see in particular page 11, line 25, to page 12, line 24).

Although D2 mentions T cells only in general, medical indications such as cancer or transplant rejection involve hyperactive T cells (see the comments on page 5, paragraph 1, lines 1 to 3, of the present application).

Consequently, the subject matter of Claims 1, 2 and 8 is anticipated in a manner prejudicial to novelty by D2.

D3 (DE-A-41 30 221) describes the use of proteolytic enzymes, such as for example papaine and/or trypsin, for treating diseases, the development of which involves proteins having a C_H2 domain. The modulation of the C_H2 structure by proteolytic enzymes could also be observed

for the membrane-constant CD 4-proteins on T lymphocytes, the effect of trypsin leading to the reduction in receptor epitope density on these cells (see in particular page 5, lines 58 to 61). Although D3 does not explicitly mention the use of proteolytic enzymes for treating hyperactive T cells, said medical indications, such as tumour diseases or viral diseases (see page 3, Table 1) imply hyperactive T cells (similarly to D2).
Therefore the subject matter of Claims 1, 2 and 8 is not considered novel over D3.

D4 (DE-A-43 02 060) discloses the use of bromelain (20 - 100 mg) alone or combined, for example, with papaine (40 - 100 mg), trypsin (10 - 30 mg), rutoside x $3H_2O$ (10 - 100 mg) for cancer treatment and/or metastases prophylaxis, bromelain causing a structural modulation of the CD44 surface molecules expressed by the cancer cells (see in particular abstract and Claims 1, 4, 8 and 9 of D4; cf. page 3, penultimate and final paragraphs and page 5, line 2, of the present application).

In Example 1 (column 3) of D4 activated T lymphocytes are brought into contact with a protease solution and the CD44 structure-modulating property of the proteases is determined by comparison of the density of the antibody-marked CD44 surface molecules on protease-treated and protease-untreated cells.

Furthermore, α_2-macroglobulin-complexed proteases are used, from which it was inferred that bromelain is not decisively inhibited by α_2-macroglobulin (see in particular Figures 5 and 6 and column 4, lines 5 to 23, of D4).

According to the present description (see in particular page 3, final paragraph) the cell surface molecule CD44 *inter alia* participates in the regulating of the limit value for T cell activation. Furthermore, hyperactive T cells are to be observed, for example, in the medical indication of cancer (see page 5, line 2, of the description).

Consequently D4, which discloses the use of bromelain for cancer treatment by modulating CD44, implicitly anticipates the novelty of the subject matter of Claims 1 to 4, 7 and 8 (as concerns tumour-antigen-specific T cells).

Furthermore, the subject matter of Claims 5 and 6 appears to be obvious (PCT Article 33(1) and (3)). The combined use of bromelain, papaine, trypsin and rutoside is known, for example, from D4 (see above). The claimed individual amounts of bromelain and rutoside per dosage unit fall within the ranges of quantities disclosed in the prior art (see, for example, D4, Claims 8 and 9). The use of 120 mg papaine and 48 mg trypsin is not associated with an unexpected effect in comparison with the maximum values of 100 mg papaine and 30 mg trypsin mentioned in the prior art (see D4 and D3) and therefore cannot be considered inventive.

2. The PCT Contracting States have no uniform criteria for assessing the industrial applicability of Claims 1 to 7 in their present form. Patentability may also depend on the wording of the claims. The EPO does not, for example, recognize the industrial applicability of claims to the medical use of a compound; it does, however, allow claims to the first medical use of a known compound or to the use of such a compound to manufacture a drug for a new medical

treatment.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
D5(Wald, M. et al.)	16 September 1999 (16.09.1999)	-	
D6(DE-A-19726255)	24 December 1998 (24.12.1998)	20 June 1998 (20.06.1998)	

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: VI

The following documents may possibly be relevant in the subsequent regional or national phase:

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The term "Phlogenzym", used several times in the description (see, for example, page 7, 5th paragraph, for example), appears to be a registered trademark. This also appears to be the case for the auxiliaries and carriers mentioned on page 7, penultimate paragraph.

2. It is not clear from the wording of Claim 8 whether this is a method for *in vitro* or *in vivo* application. In the latter case, the comments in Boxes **III** and **V, point 2**, apply similarly to Claim 8.

Patent Claims

1) Use of at least one proteolytic enzyme and, optionally, of rutoside for influencing hyperactive T cells.

2) Use according to claim 1, characterized in that trypsin, bromelain or papain or a combination of one or several of said enzymes is used as the proteolytic enzyme.

3) Use according to claim 1 or 2, characterized in that rutoside is additionally used.

4) Use according to one or several of claims 1 to 3, characterized in that 20 to 100 mg bromelain, 40 to 120 mg papain and 10 to 50 mg trypsin are used per dose unit.

5) Use according to one or several of claims 1 to 4, characterized in that 90 mg bromelain, 120 mg papain and 100 mg rutoside are used per dose unit.

6) Use according to one or several of claims 1 to 3, characterized in that 90 mg bromelain, 48 mg trypsin and 100 mg rutoside are used per dose unit.

7) Use according to one or several of claims 1 to 6, characterized in that α_2-macroglobulin is additionally used.

8) A method for influencing hyperactive cells, wherein the hyperactive cells are contacted with one or several proteolytic enzymes and, optionally, with rutoside.

PATENT
Attorney Docket No. 210445

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Ransberger et al.

Art Unit: Unassigned

Application No. Unassigned
(U.S. National Phase of PCT/EP99/07634)

Examiner: Unassigned

Filed: April 12, 2001

For: INFLUENCING HYPERACTIVE T CELLS BY PROTEOLYTIC ENZYMES

CLAIMS AS AMENDED ON APRIL 12, 2001

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

1. Canceled.

2. Canceled.

3. Canceled.

4. Canceled.

5. Canceled.

6. Canceled.

7. Canceled.

8. Canceled.

9. (New) A method of influencing hyperactive T cells, which method comprises contacting hyperactive T cells selected from the group consisting of tumor antigen-specific, transplant-specific, allergen-specific and virus-specific T cells with at least one proteolytic enzyme and, optionally, rutoside.

10. (New) The method of claim 9, wherein the at least one proteolytic enzyme is one or more of trypsin, bromelain and papain.

11. (New) The method of claim 9, wherein the hyperactive T cells are contacted with rutoside.

12. (New) The method of claim 10, wherein the hyperactive T cells are contacted with rutoside.

13. (New) The method of claim 10, wherein the hyperactive T cells are contacted with 20 to 100 mg bromelain, 40 to 120 mg papain and 10 to 50 mg trypsin per dose unit.

14. (New) The method of claim 12, wherein the hyperactive T cells are contacted with 20 to 100 mg bromelain, 40 to 120 mg papain and 10 to 50 mg trypsin per dose unit.

15. (New) The method of claim 12, wherein the hyperactive T cells are contacted with 90 mg bromelain, 120 mg papain and 100 mg rutoside x $3H_2O$ per dose unit.

16. (New) The method of claim 13, wherein the hyperactive T cells are contacted with 90 mg bromelain, 120 mg papain and 100 mg rutoside x $3H_2O$ per dose unit.

17. (New) The method of claim 14, wherein the hyperactive T cells are contacted with 90 mg bromelain, 120 mg papain and 100 mg rutoside x $3H_2O$ per dose unit.

18. (New) The method of claim 12, wherein the hyperactive T cells are contacted with 90 mg bromelain, 48 mg trypsin and 100 mg rutoside x $3H_2O$ per dose unit.

19. (New) The method of claim 9, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

20. (New) The method of claim 10, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

21. (New) The method of claim 11, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

22. (New) The method of claim 12, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

23. (New) The method of claim 13, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

24. (New) The method of claim 14, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

25. (New) The method of claim 15, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

26. (New) The method of claim 16, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

27. (New) The method of claim 17, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

28. (New) The method of claim 18, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

PATENT
Attorney Docket No. 210445

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Ransberger et al.

Art Unit: Unassigned

Application No. Unassigned
(U.S. National Phase of PCT/EP99/07634)

Examiner: Unassigned

Filed: April 12, 2001

For: INFLUENCING HYPERACTIVE T CELLS BY PROTEOLYTIC ENZYMES

CLAIMS PENDING AS OF APRIL 12, 2001

9. A method of influencing hyperactive T cells, which method comprises contacting hyperactive T cells selected from the group consisting of tumor antigen-specific, transplant-specific, allergen-specific and virus-specific T cells with at least one proteolytic enzyme and, optionally, rutoside.

10. The method of claim 9, wherein the at least one proteolytic enzyme is one or more of trypsin, bromelain and papain.

11. The method of claim 9, wherein the hyperactive T cells are contacted with rutoside.

12. The method of claim 10, wherein the hyperactive T cells are contacted with rutoside.

13. The method of claim 10, wherein the hyperactive T cells are contacted with 20 to 100 mg bromelain, 40 to 120 mg papain and 10 to 50 mg trypsin per dose unit.

14. The method of claim 12, wherein the hyperactive T cells are contacted with 20 to 100 mg bromelain, 40 to 120 mg papain and 10 to 50 mg trypsin per dose unit.

15. The method of claim 12, wherein the hyperactive T cells are contacted with 90 mg bromelain, 120 mg papain and 100 mg rutoside x $3H_2O$ per dose unit.

16. The method of claim 13, wherein the hyperactive T cells are contacted with 90 mg bromelain, 120 mg papain and 100 mg rutoside x $3H_2O$ per dose unit.

17. The method of claim 14, wherein the hyperactive T cells are contacted with 90 mg bromelain, 120 mg papain and 100 mg rutoside x $3H_2O$ per dose unit.

18. The method of claim 12, wherein the hyperactive T cells are contacted with 90 mg bromelain, 48 mg trypsin and 100 mg rutoside x $3H_2O$ per dose unit.

19. The method of claim 9, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

20. The method of claim 10, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

21. The method of claim 11, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

22. The method of claim 12, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

23. The method of claim 13, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

24. The method of claim 14, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

25. The method of claim 15, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

26. The method of claim 16, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

27. The method of claim 17, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.

28. The method of claim 18, which further comprises contacting the hyperactive T cells with α_2- macroglobulin.